UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/668,482	09/25/2000	P. Martin Petkovich	57600/00035	3039

7590 12/29/2003

JOHN C. HUNT
TORY'S LLP
SUITE3000, 79 WELLINGTON STREET WEST
BOX 270, TORONTO-DOMINION CENTRE
TORONTO, MSL1A9
CANADA

EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/668,482	PETKOVICH ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *83,90 and 113-161* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83,90 and 113-161* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/11/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The amendment filed August 11, 2003 amending claims 83 and 90, canceling claims 84-89 and 91-112 and adding claims 113-161 has been entered.

Claims 83, 90 and 113-161 are pending.

Specification

The disclosure is objected to because of the paper and computer readable forms of the Sequence Listing are not identical. The paper copy contains 35 sequences while the computer readable form has 43 sequences.

A substitute paper copy of the Sequence Listing identical to the computer readable form in the file is required. It should be accompanied by the statement the two forms are identical and by the amendment directing the entry of a substitute Sequence Listing. Applicants do NOT need to submit the computer readable form.

Claim Objections

Claims 158-161 are objected to because of the following informalities: in the expression "a non-transfected said cell", "a" and "said" appears to be incompatible.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 83, 90 and 113-161 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Independent claims 83 and 90 have been amended and new independent claims 142 and 150 have been added to recite the limitation "wherein the microsomal preparation is substantially free of other proteins that are cytochromes expressed by epidermal cells". The Examiner is unable to locate adequate support in the specification for such limitation. Thus there is no indication that "the microsomal preparation [that] is substantially free of other proteins that are cytochromes expressed by epidermal cells" was within the scope of the invention as conceived by Applicants at the time the application was filed.

Furthermore, the Examiner is unable to locate adequate support in the specification for the limitation "wherein the amino acid sequence identity between the protein and SEQ ID NO:4 is at least about 93 percent" in claim 116. Thus there is no indication that "the protein with 93 percent identity to SEQ ID NO:4" was within the scope of the invention as conceived by Applicants at the time the application was filed.

Furthermore, the Examiner is unable to locate adequate support in the specification for the limitation "wherein the preparation is enriched at least 6.3 fold in said oxidase activity with respect to a microsomal preparation obtained from a non-transfected said cell" (claims 158, 160) and the limitation "wherein the preparation is enriched at least 7.8 fold in said hydroxylase activity with respect to a microsomal preparation obtained from a non-transfected said cell" (claims 159, 161). Thus there is no indication that "the preparation [that] is enriched at least 6.3 (7.8) fold in said oxidase (hydroxylase) activity with respect to a microsomal preparation obtained from a non-transfected said cell" was within the scope of the invention as conceived by Applicants at the time the application was filed.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

Claims not specifically discussed above are rejected as dependent from a rejected base claim.

Claims 116, 120-128, 131-139, 142-147, 149-155, 157, 160 and 161 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an all-*trans* retinoic acid 4-hydroxylase encoded by SEQ ID NOs: 3, 5 or 31 or a sequence that hybridizes thereto under highly stringent conditions as well as for an all-*trans* retinoic acid 4-hydroxylase having the amino acid sequence of SEQ ID

NOs: 2, 4 or 32 or a sequence that is at least 95% identical thereto, does not reasonably provide enablement for an all-*trans* retinoic acid 4-hydroxylase having an amino acid sequence that is at least 35%, 40%, 50%, 60%, 65%, 70%, 75%, 85% or 90% identical to SEQ ID NOs: 2, 4 or 32. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Factors pertinent to this discussion include predictability of the art, guidance in the specification, breadth of claims, and the amount of experimentation that would be necessary to use the invention.

Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are

tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claim, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a great number of modifications of an all-*trans* retinoic acid 4-hydroxylase having the amino acid sequence of SEQ ID NOs: 2, 4 or 32 because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting the requisite activity;(B) the general tolerance of a protein to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a great number of amino acid modifications of SEQ ID NOs: 2, 4 or 32. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a protein having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 83, 90 and 113-161 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83, 90, 142 and 150 are unclear as reciting "a microsomal preparation comprising a recombinant protein expressed by a cell that has been transfected with ...". Amending the claims to recite "a microsomal preparation of a cell that has been transfected with a nucleic acid encoding a protein ..., said microsomal [preparation comprising said protein", for example, is suggested.

Claims 116, 120-128 depend from claim 83 and recite an amino acid sequence that "35%, 40%, 50%, 60%, 65%, 70%, 75%, 85% or 90% identical to SEQ ID NOs: 2, 4 or 32" whereas said amino acid sequence must be encoded by a nucleic acid that hybridizes to SEQ ID NOs: 3, 5 or 31" under highly stringent conditions, i.e. not encompassing such percent identity. Similarly, claims 131-139, which depend from claim 90, are indefinite.

Claim 130 depends from claim 83 and as such is drawn to a protein that "oxidizes all-*trans* retinoic acid at the C4-position of the β-ionone ring". However, claim 130 is drawn to "the protein [that] hydroxylates the C18-position of all-*trans* retinoic acid". "C18-position" is not included in the scope of claim 83 rendering the scope of claim 130 indefinite. Furthermore, claim 83 recites "oxidizes" whereas claim 130 recites "hydroxylates" without the antecedent basis. Similarly, claim 149, which depends from claim 142, is indefinite.

Claim 141 depends from claim 90 and as such is drawn to a protein that "hydroxylates all-*trans* retinoic acid at the C4-position of the β-ionone ring". However, claim 141 is drawn to "the protein [that] hydroxylates the C18-position of all-*trans* retinoic acid". "C18-position" is not included in the scope of claim 90 rendering the scope of claim 141 indefinite. Similarly, claim 157, which depends from claim 150, is indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 83, 90, 114-117 and 119-157 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duell et al.(A) in view of Roberts et al.

Duell et al. (A), (form PTO-1449 filed February 6, 2003, reference 6, J. Clin. Investigation (1992), 90,1269-1274) teach a retinoic acid induced all-*trans* retinoic acid 4-hydroxylase activity in human skin microsomes. They teach that said activity catalyzes conversion of RA to 4-OH RA and 4-oxo RA (abstract, page 1271).

Duell et al. teach with the references to the early publications by different authors that said activity occurs in different tissues such as "liver, trachea, intestine and rodent skin" (page 1269, second column). The recited references describe hamster and rat tissues.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a microsomal preparation from different human tissues. One of ordinary skill in the art would have been motivated to make preparations from various tissues, for example, as a matter of convenience depending on their availability

and in order to determine the differential tissue expression of the important activity taught by Duell et al. The microsomal preparation having the requisite activity contains a polypeptide with said activity having an inherent amino acid sequence of SEQ ID NO:4.

With regard to claims 115 and 119, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make a microsomal preparation from different mouse tissues. One of ordinary skill in the art would have been motivated to use mice as a matter of convenience since it is the most used laboratory animal whose genome is very close to human. One of ordinary skill in the art would have a reasonable expectation of success because the requisite activity has been shown in other rodents such as hamster and rat that are farther from human than mouse. The microsomal preparation having the requisite activity contains a polypeptide with said activity having an inherent amino acid sequence of SEQ ID NO:32.

The microsomal preparation from a tissue such as liver, testis or intestine would be substantially free of other proteins that are cytochromes expressed by epidermal cells.

Allowable Subject Matter

Claims drawn to a microsomal preparation comprising a polypeptide having the amino acid sequence of SEQ ID NO:2 or a sequence that is at least 95% identical to

SEQ ID NO:2 and a polypeptide encoded by SEQ ID NO:3 or a sequence that hybridizes to SEQ ID NO:3 under highly stringent conditions would be allowable.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Roberts et al. (form PTO-1449 filed February 6, 2003, reference 11, J. Biol. Chem. (1979), 254, 6303-6309) teach an all-*trans* retinoic acid 4-hydroxylase activity in hamster liver, testis and kidney (page 6306, Figure 3).

Leo et al. (form PTO-1449 filed February 6, 2003, reference 39, Arch. Biochem. Biophys. (1984), 234, 305-312) teach an all-*trans* retinoic acid 4-hydroxylase activity in rat liver microsomal preparation.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner

December 19, 2003